REMARKS

Reconsideration of the instant application in view of the following remarks is respectfully requested. As of the mailing date of the Office Action dated August 18, 2008, claims 12-14, 16, 20-22, 26-27 and 30 were pending and under examination.

Claim Rejections – 35 U.S.C. § 103

Claims 12-14, 16, 19-23, 26-27 and 30-31 stand rejected under 35 U.S.C. § 103(a) as allegedly obvious over Lanterman *et al.* (*Biochem J.* 1998 Jun 1; 332 (Pt 2):525-31), Kim *et al.* (*Genetics* 2000 Dec; 156(4):1519-29) and in view of Melendez *et al.* (*Gene* 2000 Jun 13; 251(1):19-26 and GenBank Accession No. AF266756, created 6/1/2000). In particular, in response to Applicant's reply filed October 27, 2007, the PTO asserts that Applicant's arguments are not persuasive since yeast cells are widely used as a model to express human genes for functional studies of expressed proteins or enzymes, and also asserts that the cellular components and metabolic pathways are very similar between yeast and humans. Therefore, the PTO asserts that human SK would function in yeast cells and have similar activity in yeast cells as it would in human cells. The PTO further asserts that Melendez *et al.* do indeed teach a method of inhibition of human SK in COS cells, citing Figure 4, and that Kim *et al.* and Lanterman *et al.* teach assay methods of SK by which an activator or inhibitor of SK can be evaluated in terms of S-1-P formation. As such, the PTO asserts that it would have been obvious to the skilled person to combine the teachings of Lanterman *et al.*, Kim *et al.* and Melendez *et al.* with a reasonable expectation of success, and thus, alleges that the claimed invention is obvious.

Applicant traverses the rejection for the reasons already made of record, reconsideration of which is therefore respectfully requested in view of the present Remarks, and on the following grounds.

In a recent decision, the Federal Circuit in *Takeda* upheld the non-obviousness of claims directed to a novel compound, despite the assertion that the compound represented a straightforward derivative of a known compound, the derivatization of which, supposedly, would have otherwise been "obvious to try." *Takeda Chemical Industries v. Alphapharm Pty., Ltd.*, 492 F.3d 1350 (Fed. Cir. 2007). In particular, the Federal Circuit stated in *Takeda* that there was no

evidence that the specific "compound b" in the prior art would have been selected as the lead compound, and that there existed no reason, based on what was known at the time of the invention, to perform the chemical modifications necessary to achieve the claimed compounds starting from compound b as distinct from other available starting compounds. *Id.* at 1362-1363. The Federal Circuit in *Takeda* also summarized the case law concerning *prima facie* obviousness and noted, in particular, that the test for *prima facie* obviousness was applied in *In re Deuel*, 51 F. 3d 1552 (Fed. Cir. 1995). In *Deuel* it was noted that a showing that the "prior art would have suggested making the specific molecular modification necessary to achieve the claimed invention" was required in order to find obviousness (*Takeda*, citing *In re Deuel*, 51 F.3d 1552, 1558 Fed Cir. 1995; *Dillon*, 919 F. 2d 688; *Grabiak*, 769 F.2d 729). Further, the Federal Circuit stated in *Takeda* that "While the KSR Court rejected a rigid application of the teaching, suggestion, or motivation ("TSM") test in a nonobviousness inquiry, the Court acknowledged the importance of identifying 'a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does' in an obviousness determination." (*Takeda*, citing KSR, 127 S. Ct. at 1731) (Emphasis added).

In the present case, Applicant submits that the PTO provides no reason that would have prompted a person having ordinary skill in the art to select, as a starting point from among myriad possible cell types that were available when the present application was filed, the mutant yeast strains of Kim *et al.* as a "lead compound", and then to modify them to express human SK in order to screen for SK inhibitors. No motivation or reason exists in the prior art for the person having ordinary skill to select the mutant yeast strains taught by Kim *et al.* over other available options known at that time, such as using the cell lysates described in Melendez *et al.* Applicant submits that if anything, the skilled person would have been more likely to use the cell lysate-based assay described by Melendez *et al.* because the Melendez assay would have required no modification in order to be used as a screen for SK inhibitors; the Melendez assay would also have had the added advantage of employing mammalian cell lysates. The skilled person would have selected the Melendez assay with an expectation of success because that assay was fully described by Melendez *et al.* and was already functional without requiring modification.

Furthermore, contrary to the PTO's assertion and as noted in Applicant's response filed August 13, 2008, in fact, Lanterman *et al.* provide good reason to steer the skilled person away from selecting the mutant yeast cells of Kim *et al.* in favor of the assay described by Melendez *et al.* Lanterman *et al.* disclose that (D,L)-*threo*-dihydrosphingosine, a known inhibitor of mammalian SK, failed to inhibit the yeast SK enzyme (see abstract, page 527, last paragraph and Figure 3), suggesting that molecular pathway components of the yeast sphingolipid metabolism system may have structural and functional differences from the mammalian sphingolipid metabolism system. As such, absent the teachings of the present application it could not reasonably have been predicted that a human SK would function in a yeast sphingolipid pathway. On the contrary, in view of Lanterman *et al.* the person having ordinary skill in the art would if anything have believed that human SK would be incompatible with the yeast sphingolipid metabolism pathway. The PTO thus employs impermissible hindsight in view of the instant application when the allegation is made that the presently claimed subject matter would have been obvious.

The United States Supreme Court recognized that "hindsight bias" and "ex post reasoning" are inappropriate in a determination of obviousness (*KSR v. Telflex*, 127 S. Ct. at 1742), and that a "combination of familiar elements according to known methods is likely to be obvious when it *does no more than yield predictable* results" (127 S. Ct. at 1739, emphasis added). For reasons given herein and previously made of record in the present application, the result of comparing growth of a mutant yeast strain that has been genetically altered to express a human SK to identify an agent that modulates sphingolipid metabolism was unpredictable where, in view of the state of the art, a person having ordinary skill would not have selected a yeast cell as a starting point for constructing an assay when the art pointed to more compatible mammalian systems, and would not have had the reasonable expectation of successfully incorporating human SK into a yeast sphingolipid pathway to screen for modulating agents where inhibitors of mammalian SK were ineffective in the yeast sphingolipid pathway. The Federal Circuit has recently reiterated a similar analysis concerning the nonobviousness of a claimed combination in view of its unpredictability. See *Sanofi-Synthoelabo, Inc. v. Apotex, Inc.*, 89 USPQ2d 1370 (2009, decided December 2008).

Accordingly, Applicant submits that because the prior art failed to supply the requisite reasonable expectation of success, the skilled person would not have selected the mutant yeast strains to develop an assay for screening inhibitors of human SK when another simple and viable assay already existed. Applicant therefore submits that the presently claimed invention is not obvious in view of the cited art. Reconsideration of the claims and withdrawal of the rejection are respectfully requested.

Applicant respectfully submits that all of the claims remaining in the application are now believed to be in condition for allowance. Favorable consideration and a Notice of Allowance are earnestly solicited.

The Director is authorized to charge any additional fees due by way of this Amendment, or credit any overpayment, to our Deposit Account No. 19-1090.

Respectfully submitted,

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